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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

PG3749USW

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

10/049142

INTERNATIONAL APPLICATION NO.

PCT/EP00/07669

INTERNATIONAL FILING DATE

8 August 2000

PRIORITY DATE CLAIMED

10 August 1999

TITLE OF INVENTION

USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER

APPLICANT(S) FOR DO/EO/US

CLAYTON, Nicholas Maughan, COLLINS, Susanne Denise, FOORD, Steven Michael, GIBLIN, Gerard Martin Paul

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau)
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copy of PCT Request, Publication Cover Page

10/049142

PCT/EP00/07669

PG3749USW

24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **\$1040.00**
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **\$890.00**
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **\$740.00**
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **\$710.00**
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **\$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =**CALCULATIONS PTO USE ONLY****\$890.00**

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	15 - 20 =	0	x \$18.00	\$0.00
Independent claims	8 - 3 =	5	x \$84.00	\$420.00
Multiple Dependent Claims (check if applicable)			<input type="checkbox"/>	\$0.00

TOTAL OF ABOVE CALCULATIONS =**\$1,310.00**

- ☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.

\$0.00**SUBTOTAL =****\$1,310.00**

Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00**TOTAL NATIONAL FEE =****\$1,310.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

\$0.00**TOTAL FEES ENCLOSED =****\$1,310.00**

Amount to be: refunded	\$
charged	\$

- a. ☐ A check in the amount of _____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 07-1392 in the amount of \$1,310.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 07-1392. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



23347

PATENT TRADEMARK OFFICE

SIGNATURE

Lorie Ann Morgan

NAME

38,181

REGISTRATION NUMBER

DATE

5 Feb 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

N. Clayton et al.,

Serial No.: To be Assigned

Examiner: To be Assigned

Filing Date: Concurrently Herewith

Art Unit: To be Assigned

For: USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT
OF NEUROPATHIC PAIN AND COLON CANCERCommissioner of Patents
Washington D.C. 20231PRELIMINARY AMENDMENT

Sir:

Prior to examination on the merits, please amend and consider the instant application
in view of the following amendments and remarks.

AmendmentIn the Abstract:

Please substitute the abstract provided.

In the Specification:

At page 1, line 3, please insert:

--Cross-References to Related Applications

This application is a Rule 371 Application of PCT Application No. EP00/07669, filed 8
August 2000, which claims priority to GB Application Serial No. 9918745.2, filed 10
August 1999 and GB Application Serial No. 9928437.4, filed 1 December 1999.

Background of the Invention--.

At page 1, line 14, please insert:

--Brief Summary of the Invention--.

At page 2, line 11, please insert:

--Detailed Description of the Invention--.

A marked-up copy of the amended specification is not provided herewith inasmuch as all amendments represent added language.

In the Claims:

Please cancel claims 1-4, 7-13 and 16-18. Please amend the claims as follows. Please add new claims 19-29. The following clean claims reflect the amendments being made herein. Pursuant to 37 CFR 1.121(c)(3), a marked-up copy of the amended claims is attached hereto.

5. (Amended) A method of treating neuropathic pain in a mammal comprising administering an effective amount of an EP4 receptor ligand.
6. (Amended) A method of treating colon cancer in a mammal comprising administering an effective amount of an EP4 receptor ligand.
14. (Amended) A method of treating neuropathic pain in a mammal comprising administering an effective amount of an EP4 receptor antagonist.
15. (Amended) A method of treating colon cancer in a mammal comprising administering an effective amount of an EP4 receptor antagonist.
19. (New) The method according to claim 5 wherein said mammal is man.
20. (New) The method according to claim 6 wherein said mammal is man.
21. (New) The method according to claim 5, further comprising administering one or more therapeutic agents selected from the group consisting of a cyclooxygenase 2 (COX-2) inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, non-steroidal anti-inflammatory drugs (NSAID's), a leukotriene receptor antagonist, disease modifying

anti-rheumatic drugs (DMARD's), an adenosine 1 agonist, a recombinant human tumor necrosis factor (TNF) receptor fusion protein, a sodium channel antagonist, an N-methyl D-aspartate (NMDA) antagonist, and a 5HT1 agonist.

22. (New) A pharmaceutical composition comprising an EP4 receptor ligand and a COX-2 inhibitor.

23. (New) The pharmaceutical composition according to claim 22 further comprising a pharmaceutically acceptable carrier.

24. (New) A pharmaceutical composition comprising an EP4 receptor ligand and one or more therapeutic agents selected from the group consisting of a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.

25. (New) The method according to claim 14, wherein said mammal is man.

26. (New) The method according to claim 15, wherein said mammal is man.

27. (New) A pharmaceutical composition comprising an EP4 receptor antagonist and a COX-2 inhibitor.

28. (New) The pharmaceutical composition according to claim 27 further comprising a pharmaceutically acceptable carrier.

29. (New) A pharmaceutical composition comprising an EP4 receptor antagonist and one or more therapeutic agents selected from the group consisting of a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor

fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.

Remarks

Currently Claims 5-6, 14-15, and 19-29 are pending. Claims 1-4, 7-13, and 16-18 are canceled. Claims 5-6 and 14-15 have been amended to conform the claims to standard US practice. Claims 19-29 have been added to complete the record. Support for these claims can be found in Applicants' original specification, particularly at original claims 1-18. No new matter is added.

An abstract on a separate page is provided herewith.

Applicants respectfully submit that the instant application is in condition for substantive examination, which action is respectfully requested. The Examiner is invited to contact the undersigned at 483-8222, to discuss this case further if desired.

Respectfully submitted,



Lorie Ann Morgan

Attorney for Applicants
Registration No. 38,181

Date: 5 Feb. 02
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Research Triangle Park
North Carolina 27709
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5

Express Mailing Label
EL395893471US

Marked-up Claims

5. (Amended) A method of treating neuropathic pain in a mammal[, including man,] comprising [administration of] administering an effective amount of an EP4 receptor ligand.
6. (Amended) A method of treating colon cancer in a mammal[, including man,] comprising [administration of] administering an effective amount of an EP4 receptor ligand.
14. (Amended) A method of treating neuropathic pain in a mammal[, including man,] comprising [administration of] administering an effective amount of an EP4 receptor antagonist.
15. (Amended) A method of treating colon cancer in a mammal[, including man,] comprising [administration of] administering an effective amount of an EP4 receptor antagonist.

Use of EP4 Receptor Ligands in the Treatment of, *inter alia*, Neuropathic Pain
and Colon Cancer

The present invention relates to new uses for EP4 receptor ligands.

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The EP4 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE₂. PGE₂ also has affinity for the other EP receptors (types EP1, EP2 and EP3).

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Compounds exhibiting EP4 binding activity have been described in, for example, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO98/55468, EP0855389 and EP0985663. GB2330307 describes the use of EP4 antagonists in the treatment of conditions with accelerated bone resorption.

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It has now been found that EP4 receptor ligands are of use in the treatment of neuropathic pain, colon cancer, migraine and in increasing the latency of HIV infection.

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It is believed that selective EP4 receptor ligands exhibit a number of advantages over current non-steroidal anti-inflammatory (NSAID) and cyclo-oxygenase-2 inhibitor (COX-2i) drugs which act via a number of prostaglandin pathways. By selectively binding to the EP4 receptor, the beneficial activities of other prostaglandin pathways are retained. The use according to the instant invention therefore provides greater efficacy and improved gastro-intestinal safety over NSAIDs.

25

The present invention provides the novel use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine and for increasing the latency of HIV infection.

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In a further aspect the invention provides a novel method of increasing the latency of HIV infection; and for treating migraine, neuropathic pain, and colon cancer; in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.

In a further aspect the present invention provides the novel use of an EP4 receptor antagonist in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine and for increasing the latency of HIV infection.

In a further aspect the invention provides a novel method of increasing the latency of HIV infection; and for treating migraine, neuropathic pain, and colon cancer; in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.

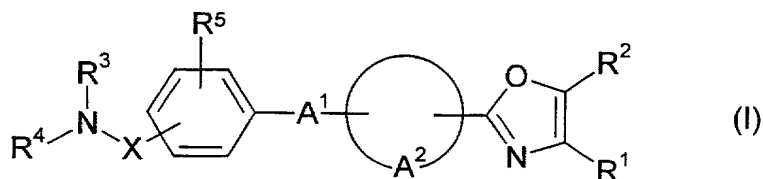
It is to be understood that reference to treatment as used herein includes treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

Suitable EP4 receptor ligands for use in the present invention include those described in GB2330307, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO98/55468, EP0855389 and EP0985663, all incorporated by reference herein. A preferred EP4 receptor ligand for use in the present invention is the compound [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid and pharmaceutically acceptable derivatives thereof of formula (IF) below.

Compounds described in GB2330307 are $[1\alpha(Z), 2\beta, 5\alpha]-(\pm)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic$ acid and the physiologically acceptable salts and solvates thereof and $[1R[1\alpha(Z), 2\beta, 5\alpha]]-(-)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic$ acid and the physiologically acceptable salts and solvates thereof.

$[1\alpha(Z), 2\beta, 5\alpha]-(\pm)-7-[5-[(1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic$ acid and the physiologically acceptable salts and solvates thereof and $[1R[1\alpha(Z), 2\beta, 5\alpha]]-(-)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic$ acid and the physiologically acceptable salts and solvates thereof may be prepared and formulated according to the methods described in UK Patent Application No GB 2075503.

Compounds described in WO00/18744 are oxazole compounds of formula (I)



5 wherein

R^1 is aryl which may be substituted with halogen(s),

R^2 is aryl which may be substituted with halogen(s),

X is single bond, C=O or SO₂,

R^3 and R^4 are independently hydrogen or suitable substituent,

(wherein X is C=O, neither R^3 nor R^4 is hydrogen),

R^3 and R^4 may be linked together to form -N \bigcirc

-N \bigcirc is N-containing heterocyclic group which may be substituted with one or more suitable substituent(s),

R^5 is

(1) hydrogen,

(2) hydroxy,

(3) carboxy, or

(4) protected carboxy,

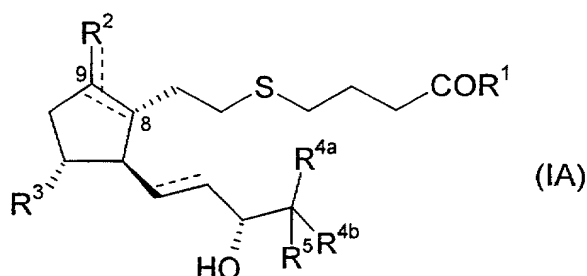
A^1 is lower alkylene or single bond,

A^2 is cyclo (C₃ - C₉) alkane or cyclo (C₅ - C₉)alkene,

20 or a pro-drug thereof, or a pharmaceutically acceptable salt thereof; which may be prepared according to the method described therein.

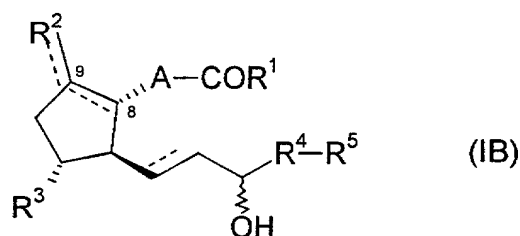
Compounds described in WO00/03980 are 5-thia- ω -substituted phenyl-prostaglandin E derivatives of formula (IA)

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wherein each symbol is as defined in the specification.

Compounds described in WO00/15608 are ω -substituted phenyl-prostaglandin E derivatives of formula (IB)



wherein each symbol is as defined in the specification.

Compounds described in WO00/21532 are

5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt,

5-butyl-2,4-dihydro-4-[[2'-[N-(2-methyl-3-furoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

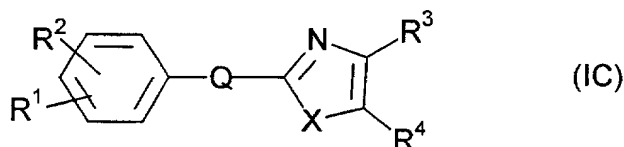
5-butyl-2,4-dihydro-4-[[2'-[N-(3-methyl-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methylpyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

and the pharmaceutically acceptable salts thereof, and mixtures thereof.

Compounds described in WO98/55468 are azole compounds of formula (IC):



wherein R¹ is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,

R² is hydrogen or lower alkyl,

R³ is aryl optionally substituted with halogen,

R⁴ is aryl optionally substituted with halogen,

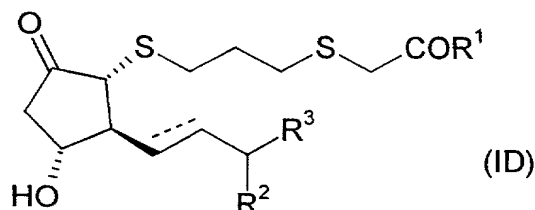
Q is $-A^1-\textcircled{A^2}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene,

$\textcircled{A^2}$ is cyclo (C₅-C₉)alkene, cyclo (C₃-C₉)alkane, bicyclo(C₆-C₉)alkene or

bicyclo (C₅-C₉)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S; which may be prepared according to the methods described therein.

Compounds described in EP0855389 are 3,7-dithiaprostanoic acid derivatives of the formula (ID):



(wherein R^1 is hydroxy, C1-4alkoxy or a group of the formula:



5 wherein R^6 and R^7 , independently, are hydrogen atom or C1-4alkyl,

R^2 is hydrogen atom or hydroxy,

R^3 is

(i) C1-8alkyl, C2-8alkenyl or C2-8alkynyl,

(ii) phenyl or C3-7cycloalkyl,

10 (iii) C1-8alkyl, C2-8alkenyl or C2-8alkynyl substituted by phenyl or C3-7cycloalkyl,

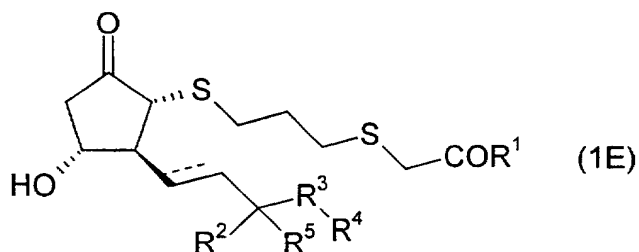
with the proviso that alkyl, alkenyl, alkynyl in (i) or (iii) may be substituted by one hydroxy group, when R^2 is hydrogen atom;

the symbol --- is a double or single bond;

the formula including the 8-epi equilibrium compound thereof);

15 a non-toxic salt thereof or a cyclodextrin clathrate thereof, which may be prepared according to the methods described therein.

Compounds described in EP0985663 are 3,7-dithiaprostanoic acid derivatives of the formula (IE)



20 wherein R^1 is hydroxy, C1-6 alkyloxy or a group of the formula:



(in which R^6 and R^7 are independently hydrogen or C1-6 alkyl);

25 R^2 is hydrogen or hydroxy;

R^3 is single bond or C1-6 alkylene;

R⁴ is

(i) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1 to 3 substituents selected from C1-6 alkyloxy and halogen atom(s),

(ii) phenyloxy or C3-7 cycloalkyloxy,

5 (iii) furyl, furyloxy, thienyl, thienyloxy, naphthyl, naphthyloxy, phthalanyl or phthalanyloxy,

(iv) phenyl, phenyloxy, C3-7 cycloalkyl or C3-7 cycloalkyloxy substituted by 1 to 3 substituents selected from the following groups:

10 C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, C1-6 alkyloxy-C1-6 alkyloxy, C2-6 alkenyloxy-C1-6 alkyl, C1-6 alkyl substituted by 1 to 3 of hydroxy, C1-6 alkyl substituted by 1 to 3 of halogen atom(s), C1-6 alkylthio, C1-6 alkylthio-C1-6 alkyl, C1-6 alkylthio-C1-6 alkyloxy, C2-6 alkenylthio-C1-6 alkyl, C1-6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro,
15 amino, hydroxy, C3-7 cycloalkyl, C3-7 cycloalkyloxy, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyloxy-C1-6 alkyl, phenyl, phenyloxy, phenyl-C1-6 alkyl, phenyl-C2-6 alkenyl, phenyl-C2-6 alkynyl, phenyloxy-C1-6 alkyl, phenyloxy-C2-6 alkenyl, phenyloxy-C2-6 alkynyl, furyl, furyloxy, furyl-C1-6 alkyl, furyloxy-C1-6 alkyl, thienyl, thienyloxy, thienyl-C1-6 alkyl and thienyloxy-C1-6 alkyl

20 (the above mentioned phenyl, furyl, thienyl and cycloalkyl being optionally substituted by 1 to 3 substituents selected from C1-6 alkyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, nitro, halogen, trihalomethyl, amino and hydroxy), or

25 (v) furyl, furyloxy, thienyl, thienyloxy, naphthyl, naphthyloxy, phthalanyl or phthalanyloxy substituted by 1 to 3 substituents selected from the following groups:

30 C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, C1-6 alkyloxy-C1-6 alkyloxy, C2-6 alkenyloxy-C1-6 alkyl, C1-6 alkyl substituted by 1 to 3 of hydroxy, C1-6 alkyl substituted by 1 to 3 of halogen atom(s), C1-6 alkylthio, C1-6 alkylthio-C1-6 alkyl, C1-6 alkylthio-C1-6 alkyloxy, C2-6 alkenylthio-C1-6 alkyl, C1-6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro, amino, hydroxy, C3-7 cycloalkyl, C3-7 cycloalkyloxy, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyloxy-C1-6 alkyl, phenyl, phenyloxy, phenyl-C1-6 alkyl, phenyl-C2-6 alkenyl, phenyl-C2-6 alkynyl, phenyloxy-C1-6 alkyl, phenyloxy-C2-6 alkenyl.

35

phenyloxy-C2-6 alkynyl, furyl, furyloxy, furyl-C1-6 alkyl, furyloxy-C1-6 alkyl, thienyl, thienyloxy, thienyl-C1-6 alkyl and thienyloxy-C1-6 alkyl (the above mentioned phenyl, furyl, thienyl and cycloalkyl being optionally substituted by 1 to 3 substituents selected from C1-6 alkyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, nitro, halogen, trihalomethyl, amino and hydroxy);

R^5 is hydrogen or C1-6 alkyl;

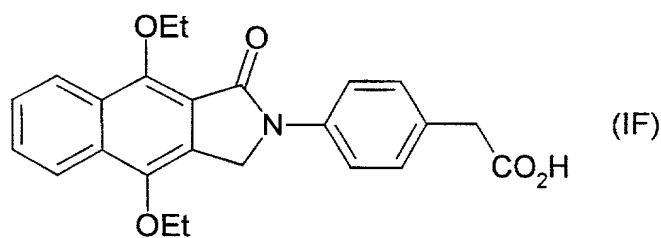
and the symbol \equiv is double bond or single bond;

the formula including the 8-epi equilibrium compound;

with the proviso that when R^2 is hydrogen, C1-6 alkylene represented by R^3 may be substituted by a hydroxy group;

or a non-toxic salt thereof or cyclodextrin clathrate thereof, which may be prepared according to the methods described therein.

As mentioned above, a preferred EP4 receptor ligand for use in the present invention is the compound [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid of formula (IF) below.



The compound of formula (IF) and pharmaceutically acceptable derivatives thereof is novel and therefore forms a further feature of the invention.

The ability of the compounds to bind to EP4 receptors may be demonstrated in the Human EP₄ Scintillation Proximity Assay.

Quantification of radioligand binding by scintillation proximity assay (SPA) is a long-established principle. Briefly, the affinity of compounds for a receptor is assessed by the specific competition between known quantities of radiolabelled

ligand and compound for that receptor. Increasing concentrations of compound reduce the amount of radiolabel that binds to the receptor. This gives rise to a diminishing scintillation signal from SPA beads coated with membranes that bear the receptor. The signal may be detected with a suitable scintillation counter and the data generated may be analysed with suitable curve-fitting software.

The human EP₄ SPA assay (hereafter referred to as 'the assay') utilises membranes prepared from Chinese Hamster Ovary (CHO cells) infected with Semliki Forest Virus (SFV). The virus is previously transfected with an SFV-1 RNA construct containing the hEP₄ receptor. Cells washed free of media are homogenised in a pH-buffered medium containing peptidase inhibitors. A suitable buffer is of the following composition: 50mM HEPES, 1mM EDTA, 25µg/ml bacitracin, 100µM leupeptin, 1mM PMSF, 2µM Pepstatin A, pH adjusted to 7.4 with KOH. Following removal of cell debris by a low-speed centrifugation, a pellet of membranes is prepared by a high-speed (48000g) centrifugation of the resulting supernatant. Membrane suspensions such as that described may be stored at -80°C until used.

For assay, membranes expressing human EP₄ receptors are diluted in a pH-buffered medium and mixed with SPA beads coated with a suitable substance to facilitate the adhesion of membranes to the beads. The concentrations of membrane protein and SPA beads chosen should result in SPA binding signal of at least 300 corrected counts per minute (CCPM) when tritiated radioligand at a concentration close to its K_d (affinity value) is combined with the mixture. Non-specific binding (nsb) may be determined by competition between the radiolabelled ligand and a saturating concentration of unlabelled ligand. In order to quantify the affinity of EP₄ receptor ligands, compounds are diluted in a stepwise manner across the wells of a 96-well plate. Radioligand, compound, and unlabelled ligand are then added to a 96-well plate suitable for the measurement of SPA binding signals prior to the addition of bead / membrane mixture to initiate the binding reaction. Equilibrium may be achieved by incubation at room temperature for 120 minutes prior to scintillation counting. The data so generated may be analysed by means of a computerised curve-fitting routine in order to quantify the concentration of compound that displaces 50% of the specific radioligand binding (IC₅₀). The affinity (pK_i) of the compound

may be calculated from the IC_{50} by application of the Cheng-Prusoff correction. Suitable reagents and protocols are: reaction buffer containing 50mM HEPES, 10mM $MgCl_2$, pH adjusted to 7.4 with KOH; SPA beads coated with wheatgerm agglutinin; 1.25nM [3H]-prostaglandin E_2 as radioligand; 10 μ M prostaglandin E_2 as unlabelled ligand; a three-fold dilution series of compound starting at 10 μ M and ending at 0.3nM is adequate.

By application of this technique, 4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid (IF) had a pK_i of 7.00 ± 0.28 (mean \pm standard deviation of the mean; $n = 87$).

The novel use of EP4 receptor ligands in the treatment of neuropathic pain has been demonstrated in the following test.

The chronic constriction injury (CCI) model was used to induce the neuropathic hypersensitivity (Bennett & Xie, 1988) in male random hooded rats.

Under isoflurane anaesthesia, the common left sciatic nerve was exposed at mid thigh level and four loose ligatures of Chromic gut tied around it. The wound was then closed and secured using suture clips. The surgical procedure was identical for the sham operated animals except the sciatic nerve was not ligated. The rats were allowed a period of seven days to recover from the surgery before behavioural testing began.

4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid (IF) (10mg/kg-1 b.i.d. PO) was dosed chronically for 14 days (days 20-33 post-operative). A reversal of the CCI-induced decrease in paw withdrawal threshold became apparent following 3 days of chronic dosing which was maximal after 1 week. This reversal was maintained throughout the remainder of the dosing period. Following cessation of the drug treatment the paw withdrawal threshold returned to that of the vehicle treated CCI-operated animals.

The compounds for use in the invention may be administered orally at a dose of from 0.1 to 10 mg/kg body weight per day and more particularly 0.3 to 3 mg/kg body weight per day, calculated as the free base. The dose range for adult

human beings is generally from 8 to 1000 mg/day, such as from 35 to 800 mg/day, preferably 20 to 200 mg/day, calculated as the free base.

5 The precise amount of the compounds administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend upon a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

10 The compounds and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

15 While it is possible for the compounds to be administered as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The formulations comprise the compounds together with one or more acceptable carriers or diluents therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

20 The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general
25 the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured

basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

5 The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

10 In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

15 The EP4 receptor ligand for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib or parecoxib; 5-lipoxygenase inhibitors; low dose aspirin; NSAID's, such as diclofenac, indomethacin or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine 1 agonists; recombinant human TNF receptor fusion proteins such as etanercept; sodium channel antagonists, such as lamotrigene; NMDA antagonists, such as glycine antagonists; and 5HT₁ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or
20 rizatriptan. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

25 The invention thus provides, in a further aspect, the use of a combination comprising an EP4 receptor ligand with a further therapeutic agent in the treatment of migraine, neuropathic pain, colon cancer and in increasing the latency of HIV infection.

30 In a further aspect, the invention provides the use of a combination comprising an EP4 receptor antagonist with a further therapeutic agent in the treatment of
35

migraine, neuropathic pain, colon cancer and in increasing the latency of HIV infection.

5 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

10 When an EP4 receptor ligand is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

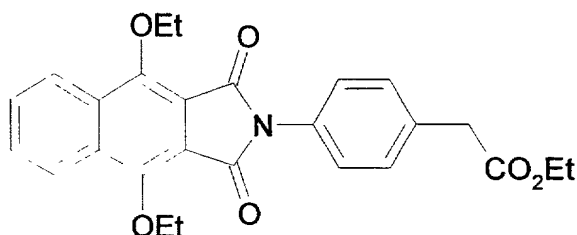
15 Likewise, when an EP4 receptor antagonist is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

20 Preferred unit dosage formulations are those containing an effective daily dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient. Conveniently that may be from 5 mg to 1000 mg, such as from 8 mg to 1000 mg, more conveniently 35 mg to 800 mg, and most conveniently 20 to 25 200 mg, calculated as the free base.

30 The compound of formula (IF) and pharmaceutically acceptable derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure.

35 A suitable method for the preparation of compound (IF) and pharmaceutically acceptable derivatives thereof is described below and forms a further aspect of the invention.

Compound (IF) may be prepared by reducing the compound



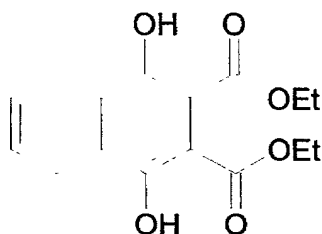
- 5 with a suitable reducing agent, for example zinc in acetic acid at elevated temperature, followed by separation of isomers and deprotection (eg. with aqueous base at elevated temperature).

10 The following Example which should not be construed as constituting a limitation thereto is provided to illustrate the invention.

15 ¹H NMR spectra were obtained at 400MHz on a Bruker DPX400 spectrophotometer. J values are given in Hz. Mass spectra were obtained on a Micromass series II MS (electrospray positive or negative).

Intermediate 1

Ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate



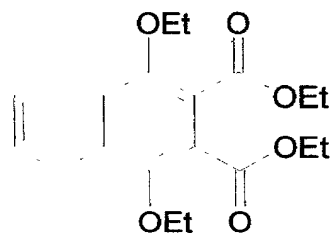
20

25 Sodium (60g, 2.6mol) was dissolved in ethanol (1.2L) and the mixture was cooled to 40°C. Diethylphthalate (960ml, 4.83mol) was added and the mixture heated under nitrogen until the temperature reached 115°C. Diethyl succinate (211.3g, 1.21mol) was added dropwise over 45 min. The reaction was heated at 115°C for a further 45 min, cooled to room temperature and poured onto water

(1.2L). Ethyl acetate (1L) was added and stirred, the layers were separated and the organics were extracted with sodium hydroxide solution (2N, 1L). The combined aqueous was acidified to pH 3 and the mixture extracted with ethyl acetate (2 x 1L). The combined organics were washed with a saturated solution of sodium hydrogen carbonate (2 x 1.5L), then brine, dried (MgSO₄), filtered and the solvent evaporated under vacuum. The residue was purified using a 2.5kg Biotage column eluting with 5% ethyl acetate / hexane to give ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate as a white solid, (60g, 16%)
 δ H CDCl₃ 10.44,(2H, s), 8.34,(2H, m), 7.68,(2H, m), 4.37,(4H, q), 1.37,(6H, t).

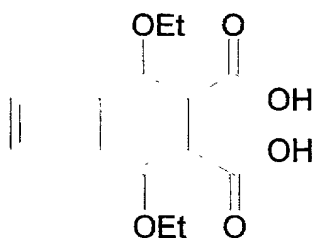
Intermediate 2

Ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate



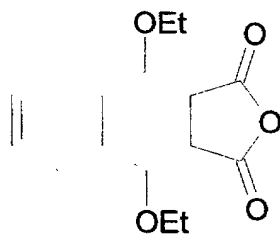
Ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate (30g, 98.6 mmol) and potassium carbonate (150g, 1.09mmol) were stirred in acetone (600ml) under nitrogen. Iodoethane (150g, 0.96mol) was added and the mixture was stirred at reflux overnight. The reaction was cooled, diluted with ethyl acetate and filtered. The filtrate was evaporated to leave a brown oil, which was dissolved in toluene and washed with potassium hydroxide solution (5%, 150ml) and brine. Drying over magnesium sulphate and evaporation of the solvent gave a yellow solid. Purification using an 800g Biotage column gave ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate as a white solid (32g, 90%).

δ H CDCl₃ 8.16,(2H, m), 7.60,(2H, m), 4.40,(4H, q), 4.18,(4H, q), 1.50,(6H, t), 1.40,(6H, t).

Intermediate 3**1,4-Diethoxy- 2,3-naphthalenedicarboxylic acid**

5 Ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate (32g, 89mmol) was added to a solution of sodium hydroxide (20g) in ethanol (200ml) and water (40ml) and stirred for 1.5h at 60°C. The reaction was cooled and the thick white suspension was filtered. The solid was dissolved in a mixture of ethyl acetate (200ml) and water (800ml). The layers were separated and the aqueous was acidified with hydrochloric acid (2M, 120ml). The aqueous was extracted with ethyl acetate (2x) and the combined organics were dried (MgSO₄). Evaporation of the solvent under vacuum gave 1,4-diethoxy- 2,3-naphthalenedicarboxylic acid as a white solid (25g, 92%).

10 δ H [²H₆] – DMSO 13.26,(2H, s), 8.15,(2H, m), 7.72,(2H, m), 4.13,(4H, q), 1.42,(6H, t).

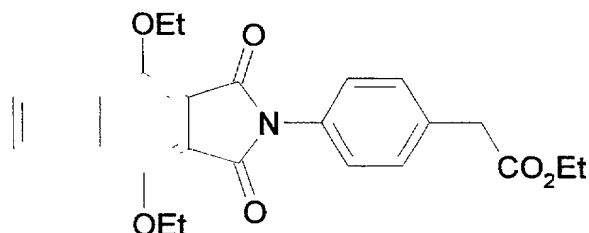
Intermediate 4**1,4-Diethoxy- 2,3-naphthalenedicarboxylic anhydride**

20 1,4-Diethoxy- 2,3-naphthalenedicarboxylic acid (25g, 82mmol) was added to a solution of thionyl chloride (23.3g) in chloroform (150ml) and stirred at reflux for 1h. The resulting solution was cooled and evaporated to dryness. Further chloroform was added and evaporation repeated to give 1,4-diethoxy- 2,3-naphthalenedicarboxylic anhydride as a yellow solid (23.3g, 99%).

25 δ H [²H₆] – DMSO 8.42,(2H, m), 7.93,(2H, m), 4.53,(4H, q), 1.46,(6H, t).

Intermediate 5

Ethyl[4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate

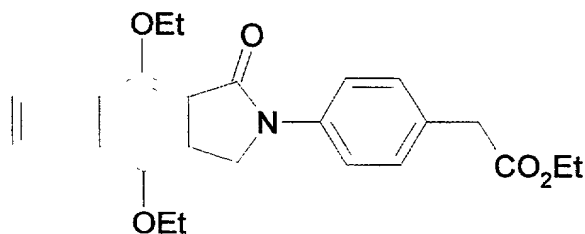


1,4-Diethoxy- 2,3-naphthalenedicarboxylic anhydride (23.3g, 81.5mmol) and ethyl (4-aminophenyl)acetate (14.8g, 82mmol) were refluxed under nitrogen in acetic acid (160ml) overnight. The mixture was cooled to room temperature and poured into water (1L). The white solid was filtered, washed with water and dissolved in dichloromethane (800ml). The solution was washed with water, brine and dried (MgSO₄) and the solvent evaporated under vacuum to give ethyl [4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate as an off-white solid (33g, 96%).

δ H [²H₆] – DMSO 8.40,(2H, m), 7.87,(2H, m), 7.42,(4H, s), 4.47,(4H, q), 4.12,(2H, q), 3.76,(2H, s), 1.45,(6H, t), 1.21,(3H, t).

Example 1 – Step 1

Ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



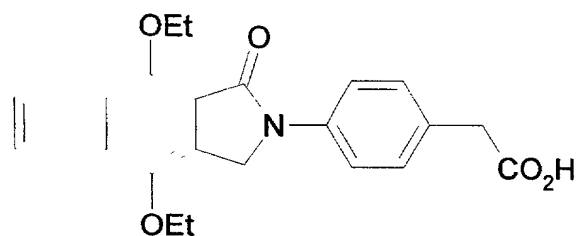
Ethyl [4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (33g, 73mmol) and zinc (90g, 1.38mol) were refluxed in acetic acid for 66h. An additional quantity of zinc (25g, 0.38mol) was added and reflux

continued for 18h. The mixture was filtered hot and the filtrate was evaporated to a yellow solid. The solid was purified by 800g Biotage column eluting with 20% ethyl acetate/ hexane to give a white solid, which was triturated in ether to give a white solid. A further fraction was obtained by crystallisation from the ether residues. A total of 10.2g, 32% of ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate was obtained.

δ H CDCl₃ 8.42,(1H, d), 8.18,(1H, d), 7.88,(2H, d), 7.63,(2H, m), 7.38,(2H, d), 5.00,(2H, s), 4.51,(2H, q), 4.26,(2H, q), 4.18,(2H, q), 3.65,(2H, s), 1.57,(6H, m), 1.28,(3H, t).

Example 1 – Step 2

[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid



Ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (5.86g, 13.5mmol) and potassium carbonate (12g) were added to a mixture of ethanol (146ml) and water (70ml) and heated to reflux for 2h. The solution was cooled to room temperature and the solvent evaporated under vacuum to leave an off-white solid. The solid was slurried in water and the water was evaporated under vacuum. The residue was stirred in hydrochloric acid (2N) for 2h, filtered and washed with water. Drying of the solid at 40° C in a vacuum oven gave [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid as a white solid (4.5g, 82%)

δ H [²H₆] – DMSO 12.27,(1H, b), 8.25,(1H, d), 8.12,(1H, d), 7.86,(2H, d), 7.61,(2H, m), 7.27,(2H, d), 5.10,(2H, s), 4.34,(2H, q), 4.25,(2H, q), 3.54,(2H, s), 1.41,(3H, t), 1.37,(3H, t). MS 406, [MH⁺]

Claims:

1. The use of an EP4 receptor ligand in the manufacture of a medicament for the treatment of neuropathic pain.
2. The use of an EP4 receptor ligand in the manufacture of a medicament for the treatment of colon cancer.
3. The use of an EP4 receptor ligand according to claims 1 or 2 wherein the EP4 receptor ligand is combined with one or more further therapeutic agents.
4. The use of an EP4 receptor ligand according to claim 3 wherein the therapeutic agents may be any of: a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.
5. A method of treating neuropathic pain in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.
6. A method of treating colon cancer in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.
7. A pharmaceutical composition comprising an EP4 receptor ligand for use in the treatment of neuropathic pain.
8. A pharmaceutical composition comprising an EP4 receptor ligand for use in the treatment of colon cancer.

9. A pharmaceutical composition comprising an EP4 receptor ligand and a COX-2 inhibitor, in combination with a pharmaceutically acceptable carrier.
- 5 10. The use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of neuropathic pain.
11. The use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of colon cancer.
- 10 12. The use of an EP4 receptor antagonist according to claims 10 or 11 wherein the EP4 receptor antagonist is combined with one or more further therapeutic agents.
- 15 13. The use of an EP4 receptor antagonist according to claim 12 wherein the therapeutic agents may be any of: a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.
- 20 14. A method of treating neuropathic pain in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.
- 25 15. A method of treating colon cancer in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.
- 30 16. A pharmaceutical composition comprising an EP4 receptor antagonist for use in the treatment of neuropathic pain.
- 35 17. A pharmaceutical composition comprising an EP4 receptor antagonist for use in the treatment of colon cancer.

18. A pharmaceutical composition comprising an EP4 receptor antagonist and a COX-2 inhibitor, in combination with a pharmaceutically acceptable carrier.

DECLARATION FOR "371" APPLICATION

**COMBINED DECLARATION FOR UTILITY or DESIGN
PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER
PG3749USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one)		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

**23347**

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Direct Telephone Calls to:

Lorie Ann Morgan
919-483-8222

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	CLAYTON	Nicholas	Maughan
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3		POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
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DECLARATION FOR "371" APPLICATION

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEYATTORNEY'S DOCKET
PG3749USWFirst Names Inventor
CLAYTON***Complete if known:***
App No.:

Filing Date

Group Art Unit:

() Declaration submitted with initial filing or

() Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER

the specification of which (check only one item below):

[] is attached hereto.

OR

[X] was filed on _____ as United States application Serial No. or PCT International

Application Number EP00/07669 filed 8 August 2000 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY)	PRIORITY CLAIMED
1. 9918745.2	GB	08/10/1999	x
2. 9928437.4	GB	12/01/1999	x
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
2.		
3.		
4.		

DECLARATION FOR "371" APPLICATION

2	FULL NAME OF INVENTOR	FAMILY NAME GIBLIN	FIRST GIVEN NAME Gerard	SECOND GIVEN NAME/INITIAL Martin, Paul
0	INVENTOR'S SIGNATURE			<u>DATE:</u>
4	RESIDENCE & CITIZENSHIP	CITY Welwyn	STATE OR FOREIGN COUNTRY Hertfordshire, GB	COUNTRY OF CITIZENSHIP GB
	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709 US

DECLARATION FOR "371" APPLICATION

**COMBINED DECLARATION FOR UTILITY or DESIGN
PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER
PG3749USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one)		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office (List name and registration number)

**23347**

PATENT TRADEMARK OFFICE

Send Correspondence to:

**23347**

PATENT TRADEMARK OFFICE

Direct Telephone Calls to:

Lorie Ann Morgan
919-483-8222

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			DATE:
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			DATE:
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			DATE:
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEYATTORNEY'S DOCKET
PG3749USWFirst Names Inventor:
CLAYTON**Complete if known:**
App No.:

Filing Date

Group Art Unit:

() Declaration submitted with initial filing or

() Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER

the specification of which (check only one item below):

[] is attached hereto.

OR

[X] was filed on _____ as United States application Serial No. or PCT International

Application Number EP00/07669 filed 8 August 2000 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

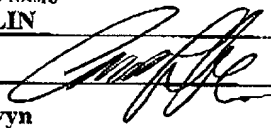
PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY)	PRIORITY CLAIMED
1. 9918745.2	GB	08/10/1999	x
2. 9928437.4	GB	12/01/1999	x
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		

DECLARATION FOR "371" APPLICATION

2	FULL NAME OF INVENTOR	FAMILY NAME GIBLIN	FIRST GIVEN NAME Gerard	SECOND GIVEN NAME/INITIAL Martin, Paul
0	INVENTOR'S SIGNATURE			DATE: 31 st January 2002
0	RESIDENCE & CITIZENSHIP	CITY Welwyn	STATE OR FOREIGN COUNTRY Hertfordshire, GB	COUNTRY OF CITIZENSHIP GB
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709 US

DECLARATION FOR "371" APPLICATION

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PATENT APPLICATION WITH POWER OF ATTORNEY** ContinuedATTORNEY'S DOCKET NUMBER
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PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

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2 0 1	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	CLAYTON	Nicholas	Maughan
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Stevenage	Hertfordshire, GB	GB
		POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
		GlaxoSmithKline	Research Triangle Park	NC 27709 US
		Five Moore Drive, PO Box 13398		
2 0 2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	COLLINS	Susanne	Denise
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	Stevenage	Hertfordshire, GB	GB
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		Five Moore Drive, PO Box 13398		
2 0 3	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	FOORD	Steven	Michael
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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CLAYTONComplete if known:
App No.:

Filing Date

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**USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON
CANCER**

the specification of which (check only one item below):

☐ is attached hereto.

OR

☒ was filed on _____ as United States application Serial No. or PCT InternationalApplication Number EP00/07669 filed 8 August 2000 and was amended on (MM/DD/YYYY) _____ (if applicable)

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0	INVENTOR'S SIGNATURE			<u>DATE:</u>
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	INVENTOR'S SIGNATURE	CLAYTON	Nicholas	Maughan
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STEVENAGE	Hertfordshire, GB CBN	GB
		GlaxoSmithKline	Research Triangle Park	NC 27709 US
		Five Moore Drive, PO Box 13398		
9	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	COLLINS	Susanne	Denise
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STEVENAGE	Hertfordshire, GB CBN	GB
		GlaxoSmithKline, Inc.	Research Triangle Park	NC 27709 US
		Five Moore Drive, PO Box 13398		
300	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	FOORD	Steven	Michael
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STEVENAGE	Hertfordshire, GB CBN	GB
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DECLARATION FOR "371" APPLICATION

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	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709 US